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Effect of insulinopenia and adrenal hormone deficiency on acute potassium tolerance

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Effect of insulinopenia and adrenal hormone deficiency on acute potassium tolerance. The ability to dispose of an acute intravenous potassium load was examined in glucocorticoid-replaced adrenalectomized rats and in rats made insulinopenic with somatostatin. Adrenalectomy resulted in a significantly greater rise in plasma potassium concentration compared with controls (1.46 ± 0.11 vs. 0.92 ± 0.05 mEq/liter, $P < 0.001$) despite the excretion of an identical percentage (47%) of the administered potassium load in 2 hours. Somatostatin-induced insulinopenia (insulin levels decreased from 37 ± 5 to 20 ± 3 μU/ml) was also associated with a significantly greater increment in plasma potassium concentration (1.51 ± 0.20 mEq/liter, $P < 0.001$) compared with controls, despite the excretion of a similar amount (39%) of the administered potassium load. In animals with combined adrenal and insulin deficiency, the rise in plasma potassium concentration occurred earlier and remained elevated for a more prolonged period of time compared with animals with either adrenalectomy or insulinopenia alone. *Conclusion.* During acute potassium loading in the rat, insulin and adrenal hormones play an important role in maintaining normal potassium homeostasis, primarily by enhancing potassium uptake by extrarenal tissues.

Effet de l'insulinopénie et du déficit en hormones surrénaliennes sur la tolérance aiguë au potassium. La capacité de disposer d'une charge intraveineuse aiguë de potassium a été étudiée chez des rats surrénalectomisés, compensés en glucocorticoïdes, et chez des rats rendus insulinopéniques par la somatostatine. La surrénalectomie a eu pour conséquence une augmentation du potassium plasmatique significativement plus grande que celle des contrôles (1,46 ± 0,11 au lieu de 0,92 ± 0,05 mEq/liter, $P < 0,001$) malgré l'excrétion en deux heures d'une fraction identique (47%) du potassium administré. L'insulinopénie déterminée par la somatostatine (insulinémie diminuée de 37 ± 5 à 20 ± 3 μU/ml) était aussi associée à une augmentation significativement plus grande de la concentration du potassium plasmatique (1,51 ± 0,20 mEq/liter, $P < 0,001$), par comparaison aux contrôles, malgré l'excrétion d'une fraction semblable (39%) de la charge de potassium administrée. Chez les animaux ayant à la fois l'insuffisance surrénale et le déficit en insuline l'augmentation du potassium plasmatique s'installe plus tôt et dure plus longtemps que chez ceux n'ayant que l'insuffisance surrénale de l'insulinopénie. *Conclusion.* Au cours de la charge aiguë en potassium chez le rat l'insuline et les hormones surrénaliennes jouent un rôle important dans l'homéostasie du potassium, essentiellement en augmentant la captation de potassium par les tissues autres que le rein.

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Hyperkalemia in association with hypoaldosteronism and normal or only mildly reduced renal function has been reported with increasing frequency in patients with diabetes mellitus [1, 2]. Although both aldosterone [3, 4] and insulin [5, 6] are known to play important roles in overall potassium homeostasis, the relative contribution of insulin versus aldosterone deficiency in the development of hyperkalemia in this syndrome has not been defined nor has the site (renal versus extrarenal) of impaired potassium tolerance been localized. Chronic adenalectomy is known to result in hyperkalemia [7, 8] and a decreased distal tubular potassium gradient [9, 10], which can be corrected by exogenous aldosterone [9]. Renal potassium excretion, however, may not be the most important defense against hyperkalemia following acute potassium loads. In human subjects, less than 50% of an acute potassium load is excreted within the 4 to 6 hours following administration, the remainder being translocated into cells [11]. Although aldosterone has been shown to affect potassium uptake by rat diaphragm muscle in vitro [12], its role in extrarenal potassium disposal during acute potassium chloride loading in vivo has not been systematically examined. In contrast, insulin has been shown to enhance cellular uptake of potassium both in vivo and in vitro [5, 6, 13–15], but its effect on renal potassium excretion is less clear [16]. Furthermore, the interaction of combined insulin-aldosterone deficiency on both renal as well as extrarenal mechanisms of acute potassium homeostasis has not previously been studied.

Methods

Male Sprague-Dawley rats (Charles River Laboratories, Boston, Massachusetts) were divided into five experimental groups as described below. All rats were maintained on 15 g of standard Purina rat chow (total daily sodium and potassium intake equal to 2.4 and 4.0 mEq/day, respectively) for 14

days prior to study. At the end of this period, a 24-hour urine sample from each rat was collected under mineral oil for determination of sodium and potassium excretion. On the day of study, a clearance experiment with acute potassium chloride loading was performed in each animal.

Group 1: Normal controls. Seventeen normal rats underwent a clearance study (Fig. 1) with potassium chloride loading. Each animal was anesthetized with Inactin® (Promonta, Hamburg, Germany), 12 mg/dg of body wt i.p., and a tracheostomy tube was inserted to insure adequate ventilation. The left carotid artery and right external jugular vein were then cannulated with PE-50 tubing for withdrawal of blood samples and experimental infusion, respectively. Transabdominal catheterization of the bladder was performed to allow complete collection of urine. Surgical fluid losses were replaced with 0.15 M sodium chloride (1% body wt), following which a constant infusion of 0.15 M sodium chloride was begun and maintained at 3.3 ml/hr except during potassium chloride administration. The GFR was determined by the clearance of tritiated methoxyinulin (New England Nuclear, Boston, Massachusetts), which was continuously infused at 20 μCi/hr following a priming dose of 30 μCi. Body temperature was maintained between 37 and 38° C by means of a warming board.

After an equilibration period of 60 min, a clearance study involving six 30-min urine collections was carried out (Fig. 1); carotid blood samples (0.2 ml each) were withdrawn at the midpoint of each urine collection for determination of plasma sodium and potassium concentrations and inulin radioactivity. During the first hour (baseline period) of the clearance study, the maintenance 0.15 M sodium chloride infusion was continued for the first two urine collections. This infusion was then replaced with an infusion of 0.121 M potassium chloride and 0.03 M sodium chloride, also administered intravenously at 3.3 ml/hr to deliver 0.4 mEq of potassium isotonically during the second hour (potassium chloride period). Again two 30-min urine samples were collected. In the third hour (post-potassium chloride period) the potassium chloride infusion was replaced with the maintenance 0.15 M sodium chloride infusion, and the final two 30-min urine collections were performed.

Group 2: Adrenalectomized rats. Eight rats were bilaterally adrenalectomized 15 days prior to clearance studies. On the day of adrenalectomy, each of these rats received glucocorticoid replacement in the form of 40 μg of dexamethasone i.p. Thereafter,

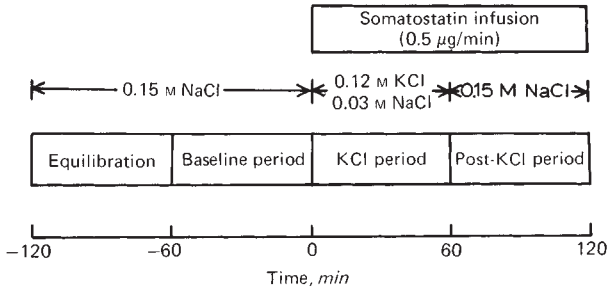

Fig. 1. *Experimental protocol.* Only groups 3 and 4 received the somatostatin infusion.

replacement was 10 μg of dexamethasone each morning until the day of the clearance study. This daily dexamethasone dose is equivalent in glucocorticoid activity to the daily corticosterone production of the rat [17]. No mineralocorticoid replacement was given. After adrenalectomy, these animals were maintained on the standard 15 g of diet as described above and allowed free access to a 0.9% sodium chloride and 2.5% dextrose drinking solution. The drinking bottles were weighed at the beginning and end of each 24-hour collection to determine sodium intake. Clearance studies performed 2 weeks after adrenalectomy were identical to that described for group 1 except that all adrenalectomized rats received dexamethasone (50 μg/dg body wt i.p.) 2 hours before surgery. This dose of dexamethasone has been shown to have no effect on renal electrolyte handling in the rat [18, 19].

Group 3: Somatostatin-infused normal rats. Eight rats were treated identically to the normal controls except for administration of somatostatin during the potassium chloride and post-potassium chloride periods (Fig. 1). Cyclic somatostatin (Ciba, Summit, New Jersey) infusion was begun at 0.5 μg/min simultaneously with the potassium chloride infusion. The somatostatin was dissolved in the experimental potassium chloride and sodium chloride solutions so that the volume of fluid administered to these animals was identical to that received by controls.

Group 4: Somatostatin-infused adrenalectomized rats. Ten rats were treated identically to the adrenalectomized (group 2) rats except for administration of somatostatin during the potassium chloride and post-potassium chloride periods, as described above.

Group 5: Normal rats receiving high sodium infusion. To increase urinary sodium excretion to rates comparable to those observed in adrenalectomized rats, we infused six normal rats with the

maintenance 0.15 M sodium chloride solution at a rate of 4.62 ml/hr during all periods except the potassium chloride period. During the potassium chloride period, a 0.087-M potassium and 0.06-M sodium chloride solution was infused at 4.62 ml/hr to deliver a total dose of 0.4 mEq of potassium. Prior to the clearance study, these animals were treated identically to the normal controls.

In four rats from each of the five groups, arterial pH was determined at the midpoint of the baseline, potassium chloride, and post-potassium chloride periods. Capillary collection tubes were sealed immediately and kept on ice until the pH was measured on a microelectrode pH meter (Radiometer, Copenhagen, Denmark). In control (group 1) and somatostatin-infused (group 3) rats, plasma glucose and insulin concentrations were determined during the baseline period and at the end of the potassium chloride period.

Analytical methods. Tritiated inulin activity was determined in a liquid scintillation counter (Packard Tri-Carb, Downers Grove, Illinois). Urine and plasma sodium and potassium concentrations were measured with a flame photometer using an internal lithium standard (Instrumentation Laboratories, Watertown, Massachusetts). Plasma glucose concentration was measured on a glucose analyzer (Beckman Instruments, Cedar Grove, New Jersey), and plasma insulin concentration was measured by radioimmunoassay, with talc to separate free from bound insulin [21].

Calculations. In the analysis of the data, urinary excretion rates for electrolytes and values of inulin clearance (GFR) were calculated by standard formulae. The mean plasma potassium concentration obtained during the baseline period was subtracted from the peak plasma potassium concentration (which occurred during the second half hour of the potassium chloride period in every animal studied) to determine the peak increment in plasma potassium. The mean rate of potassium excretion during the baseline period, as well as the peak rate of excretion (which also occurred during the second half hour of the potassium chloride period in every rat), was calculated and compared for each group. The percentage of the potassium load excreted during the 2 hours of the potassium chloride and post-potassium chloride periods was calculated as the sum of the mean increments in potassium excretion above baseline in each of these two periods divided by the administered potassium load (0.4 mEq).

The integrated area under the curve plotting the rise in plasma potassium concentration with time was calculated by the trapezoidal rule approximation and was carried out by computer (subroutine QAOIAS of the Harwell Subroutine Library of the Yale University, IBM 370/158). It is expressed as mEq/liter × min.

Statistical differences between groups were analyzed by the unpaired Student's *t* test, and the linear regression test was used to analyze statistical correlations between different parameters [22]. All data are expressed as the means ± SEM.

Results

Body weights. The body weights in groups 1 to 5 were 234 ± 8, 245 ± 9, 223 ± 7, 222 ± 6, and 235 ± 10 g, respectively.

Arterial pH. The arterial pH during the baseline period was similar (7.39 to 7.41) in all groups, and no change in pH occurred in any group during the remainder of the clearance study.

Glucose and insulin levels with somatostatin infusion. In the group 1 control rats, the plasma glucose and insulin concentrations (132 ± 5 mg/dl and 45 ± 3 μU/ml) during the potassium chloride period were similar to the baseline period (126 ± 4 mg/dl and 40 ± 5 μU/ml). In rats receiving somatostatin plus potassium chloride, a 46% decline in plasma insulin concentration from basal levels (37 ± 5 to 20 ± 3 μU/ml, $P < 0.01$) occurred, as well as a small decrease in plasma glucose concentration (116 ± 3 to 101 ± 5 mg/dl; $P < 0.05$).

Twenty-four-hour electrolyte excretion. The mean 24-hour urinary potassium excretion of 3.71 ±0.11 mEq in normal animals (groups 1, 3, and 5) was similar to the daily excretion of 3.90 ± 0.11 mEq in adrenalectomized animals (groups 2 and 4). No normal or adrenalectomized rat differed in its 24-hour potassium excretion by more than 20% from its intake (4.0 mEq/day), indicating that all animals were in potassium balance.

The 24-hour urinary sodium excretion of 14.3 ± 1.8 mEq/day in adrenalectomized rats was significantly higher than it was in controls (2.3 ± 0.07 mEq/day). This was due primarily to the higher sodium intake in adrenalectomized rats, which varied from 10 to 21 mEq/day compared to 2.4 mEq/day in normal controls. No normal or adrenalectomized rat differed in its sodium excretion by more than 18% from its individually calculated intake.

Glomerular filtration rate and urinary sodium excretion (Table 1). The GFR in the adrenalectomized groups (2 and 4), which had been maintained on a saline drinking solution, was slightly higher during the baseline period than it was in any of the other

three groups (1, 3, 5) which drank only tap water. During the potassium chloride and post-potassium chloride period, GFR was slightly less in somatostatin-infused normals (group 3) compared with controls (group 1), but the difference was small (Table 1). In all groups, GFR decreased by approximately 20% during the clearance study.

Baseline urinary sodium excretion in the adrenalectomized groups (groups 2 and 4) was significantly higher than that in the control (group 1) and somatostatin-infused (group 3) groups but similar to the excretion rate found in group 5 controls rats, which received the higher infusion rate of sodium chloride. During potassium chloride administration, the sodium excretion rose by 10 to 30% in all groups and then fell by about 50% during the post-potassium chloride period.

Plasma potassium concentration (Table 2; Fig. 2). The mean baseline plasma potassium concentration in the two groups of adrenalectomized rats

Table 1. Glomerular filtration rate and sodium excretion rate during clearance study[a]

Groups	GFR *ml/min*			$U_{Na}V$ *μEq/min*		
	Baseline	KCl	Post-KCl	Baseline	KCl	Post-KCl
1 (controls)	2.99 ±0.11	2.83 ±0.09	2.50 ±0.11	4.43 ±0.72	6.38 ±0.56	3.77 ±0.26
2 (adrenalectomy)	3.43 ±0.01	3.14 ±0.18	2.74 ±0.10	9.76 ±0.99	10.59 ±0.90	5.26 ±0.65
3 (somatostatin)	2.91 ±0.16	2.36 ±0.11	2.09 ±0.11	4.40 ±1.26	5.60 ±1.25	2.63 ±0.46
4 (somatostatin + adrenalectomy)	3.56 ±0.16	3.13 ±0.11	2.80 ±0.15	9.66 ±0.63	11.10 ±0.55	5.20 ±0.57
5 (high sodium controls)	2.75 ±0.08	2.60 ±0.10	2.37 ±0.07	7.26 ±1.00	10.85 ±1.03	5.27 ±0.66
		P values				
Con vs. ADX	<0.01	NS	NS	<0.001	<0.001	<0.05
Con vs. SRIF	NS	<0.05	<0.02	NS	NS	<0.05
Con vs. SRIF + ADX	<0.01	<0.05	NS	<0.001	<0.001	<0.05
ADX vs. SRIF	<0.02	<0.01	<0.01	<0.01	<0.01	<0.01
ADX vs. ADX + SRIF	NS	NS	NS	NS	NS	NS
SRIF vs. ADX + SRIF	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
High sodium con vs. con	NS	NS	NS	<0.05	<0.005	<0.05
High sodium con vs. ADX	<0.001	<0.05	<0.02	NS	NS	NS

[a] All values represent the means ± SEM. Abbreviations are Con, controls; ADX, adrenalectomy; SRIF, somatostatin.

Table 2. Plasma potassium concentrations (P_K) during clearance studies[a]

Groups	Baseline P_K *mEq/liter*	Peak P_K *mEq/liter*	Peak increment potassium *mEq/liter*	Post-KCl P_K *mEq/liter*
1 (controls)	4.02 ±0.05	4.95 ±0.07	0.92 ±0.05	4.19 ±0.06
2 (adrenalectomy)	4.35 ±0.07	5.81 ±0.14	1.46 ±0.11	4.95 ±0.08
3 (somatostatin)	4.09 ±0.07	5.60 ±0.18	1.51 ±0.20	4.60 ±0.05
4 (somatostatin + adrenalectomy)	4.56 ±0.15	6.21 ±0.21	1.66 ±0.07	5.55 ±0.23
5 (high sodium controls)	3.95 ±0.22	4.98 ±0.08	1.03 ±0.08	4.33 ±0.06
		P values		
Con vs. ADX	<0.001	<0.001	<0.001	<0.001
Con vs. SRIF	NS	<0.005	<0.001	<0.001
Con vs. SRIF + ADX	<0.005	<0.001	<0.001	<0.001
ADX vs. SRIF	<0.05	NS	NS	NS
ADX vs. ADX + SRIF	NS	NS	NS	<0.05
SRIF vs. ADX + SRIF	<0.01	<0.05	NS	<0.001
High sodium con vs. con	NS	NS	NS	NS
High sodium con vs. ADX	<0.001	<0.001	<0.001	<0.001

[a] All values represent the means ± SEM. Abbreviations are defined in Table 1.

(groups 2 and 4), 4.42 ± 0.09 mEq/liter, was slightly but significantly higher ($P < 0.001$) than that in group 1 control rats (4.02 ± 0.05 mEq/liter). Baseline plasma potassium concentration in somatostatin-infused rats (group 3) and in rats receiving the higher infusion rate of sodium chloride (group 5) was similar to control rats.

Following potassium chloride infusion, plasma potassium rose to peak value of 5.81 ± 0.14 mEq/liter in the adrenalectomized rats (group 2) compared to 4.95 ± 0.07 mEq/liter in the group 1 controls ($P < 0.001$). The peak increment in plasma potassium concentration was 1.46 : 0.11 mEq/liter in this adrenalectomized group versus 0.92 ± 0.05 mEq/liter in the control group ($P < 0.001$; Fig. 2). During the post-potassium chloride period, the plasma potassium concentration in these adrenalectomized rats, 4.95 ± 0.08 mEq/liter, remained significantly higher than it was in controls, 4.19 ± 0.06 mEq/liter ($P < 0.001$). In addition, the incremental area in plasma potassium concentration above baseline was significantly higher in adrenalectomized rats (91.5 ± 6.2 mEq/liter × min) compared to controls (53.2 ± 3.7 mEq/liter × min; $P < 0.001$).

Infusion of somatostatin with potassium chloride into normal rats (group 3) resulted in a significant increase in both the peak plasma potassium concentration, 5.60 ± 0.18 mEq/liter, and the peak increment in plasma potassium concentration above baseline, 1.51 ± 0.20 mEq/liter (Fig. 2), compared with control rats receiving potassium chloride alone ($P < 0.001$). The peak increase in plasma potassium concentration in somatostatin-infused rats, as well as the incremental area in plasma potassium concentration above baseline (92.2 ± 9.9 mEq/liter × min; $P < 0.005$ compared with controls), was similar to that observed in adrenalectomized animals receiving potassium chloride without somatostatin.

When potassium chloride plus somatostatin was infused into adrenalectomized rats (group 4), the increments in plasma potassium concentration above basal during the first 30 min of potassium chloride and during the entire post-potassium chloride period was significantly higher ($P < 0.05$) compared with the rise in either the adrenalectomized rats (group 2) or the somatostatin-infused rats (group 3; Fig. 2). The peak increment in plasma potassium concentration in somatostatin-infused adrenalectomized rats, 1.66 ± 0.07 mEq/liter (Fig. 2), tended to be higher than it was with either somatostatin or adrenalectomy alone. The integrated area for the rise in plasma potassium concentration above baseline was significantly higher in animals with combined deficiency (118.6 ± 4.2 mEq/liter × min) compared to animals with either adrenalectomy alone (91.5 ± 6.2 mEq/liter × min; $P < 0.005$) or insulinopenia alone (92.2 ± 9.9 mEq/liter × min; $P < 0.05$).

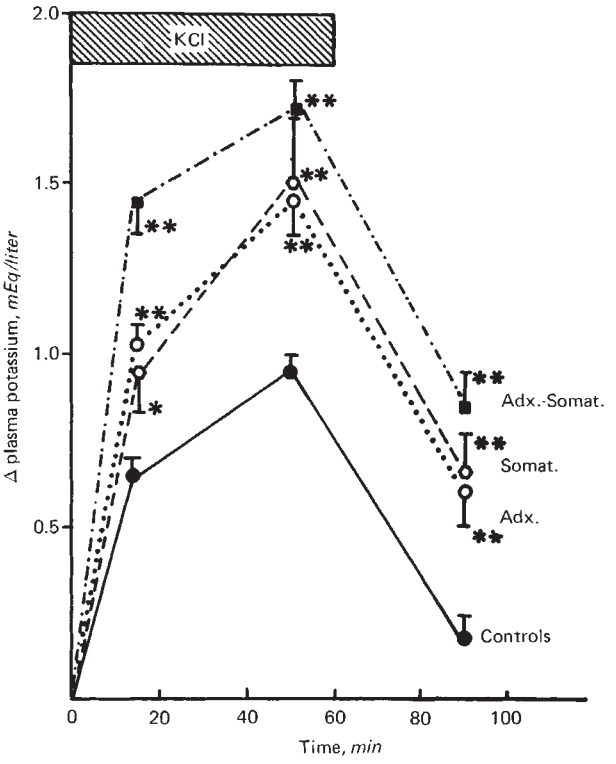

Fig. 2. *The increment in plasma potassium concentration above baseline in control (●—●), somatostatin-infused (⬠--⬠), adrenalectomized (○····○), and adrenalectomized rats receiving somatostatin (■—·—■).* The potassium chloride (0.4 mEq) was infused from 0 to 60 min. All values represent the mean ± SEM. One asterisk (*) indicates $P < 0.05$. Two asterisks (**) indicate $P < 0.005$ compared with the value in control rats.

The plasma potassium concentration in the high-sodium-infusion normal rats (group 5) was similar to that in the normal controls at every point in the clearance study and was consistently less than that of the adrenalectomized animals ($P < 0.01$).

Urinary potassium excretion (Table 3). Baseline and peak urinary potassium excretion rates, as well as the percent of the potassium load excreted in 2 hours (39 to 52%), were similar in all groups. Of particular note is that the potassium excretion rate, as well as the percent of potassium chloride load excreted in adrenalectomized rats (group 2) was similar to that in controls.

A significant correlation ($P < 0.01$) between urinary potassium excretion and plasma potassium concentration was observed in all groups except in group 4 where considerable scatter of the points ex-

isted. The slope of the regression line relating urinary potassium excretion to plasma potassium concentration in group 2 adrenalectomized rats (1.32 ± 0.43) tended to be less than that found in group 5 rats (2.42 ± 0.68) despite similar high rates of sodium excretion, but this difference did not reach statistical significance. The slope of the line in group 3 somatostatin-infused rats (1.55 ± 0.34) was similar to that found in group 1 control rats (1.64 ± 0.33).

Plasma potassium increment per amount of potassium retained (Fig. 3). To factor for small variations in urinary potassium excretion between groups, we factored the integrated rise in plasma potassium concentration above baseline in each rat by the amount of potassium retained by that rat. This expression provides an index of extrarenal potassium tolerance in each animal. The integrated rise in plasma potassium concentration was obtained by determining the area under the curve of the rise in plasma potassium concentration with time. The rise in plasma potassium concentration per amount of potassium retained was significantly higher ($P < 0.005$) in adrenalectomized rats (418 ±43 min/liter) and insulinopenic rats (408 ± 67 min/liter) compared to control animals (231 ± 25 min/liter) (Fig. 3). When combined insulin and adrenal insufficiency was created, the delta plasma potassium concentration per amount of potassium retained (624 ± 59 min/liter) was again higher ($P < 0.001$) than it was in control animals and was also higher ($P < 0.05$) than the value obtained in animals receiving either adrenalectomy alone or insulinopenia alone.

Discussion

The present study demonstrates that both adrenal hormones and insulin play important roles in the disposal of an acute potassium load and that a major site of their action is exerted on extrarenal tissues to enhance cellular uptake of potassium. In chronically adrenalectomized rats and in rats made insulinopenic with somatostatin, the increment in plasma potassium concentration following intravenous potassium chloride administration was higher than it was in control animals, despite a urinary potassium excretion rate that was similar to controls.

The role of aldosterone in the renal contribution to chronic potassium homeostasis is well established [8, 20]. Its ability to augment renal potassium excretion during acute potassium chloride loading, however, is less certain [23]. Alexander and Levinsky [24] suggested an extrarenal role for aldosterone in acute potassium homeostasis. In their studies, rats preconditioned with a high-potassium diet displayed enhanced potassium tolerance to an acute potassium chloride load compared with controls fed a normal diet. This effect could be demonstrated both in the presence and absence of kidneys, could be abolished by adrenalectomy, and could be simulated by high (but now low) doses of mineralocorticoid. An extrarenal effect of aldosterone in vitro has also been demonstrated by Adler [12] and Lim and Webster [25] using the rat hemidiaphragm preparation.

The present results lend further support to the concept that aldosterone exerts a major effect on extrarenal potassium disposal following acute po-

Table 3. Urinary potassium excretion (U_KV) during clearance studies[a]

Groups	U_KV *μEq/min*			Potassium load excreted *%*
	Baseline	Peak	Post-KCl	
1 (controls)	2.06 ± 0.14	5.19 ± 0.12	2.82 ± 0.12	47.3 ± 6
2 (adrenalectomy)	2.37 ± 0.22	5.53 ± 0.22	3.39 ± 0.11	47 ± 5
3 (somatostatin)	2.29 ± 0.14	5.04 ± 0.30	2.98 ± 0.24	39 ± 5
4 (somatostatin > adrenalectomy)	2.45 ± 0.26	5.54 ± 0.27	3.52 ± 0.20	52 ± 5
5 (high sodium controls)	2.05 ± 0.18	4.92 ± 0.24	2.80 ± 0.27	42 ± 7
	P values			
Con vs. ADX	NS	NS	<0.005	NS
Con vs. SRIF	NS	NS	NS	NS
Con vs. SRIF + ADX	NS	NS	<0.01	NS
ADX vs. SRIF	NS	NS	NS	NS
ADX vs. ADX + SRIF	NS	NS	NS	NS
SRIF vs. ADX + SRIF	NS	NS	NS	NS
High sodium con vs. con	NS	NS	NS	NS
High sodium con vs. ADX	NS	NS	NS	NS

[a] All values represent the means ± SEM. Abbreviations are defined in Table 1.

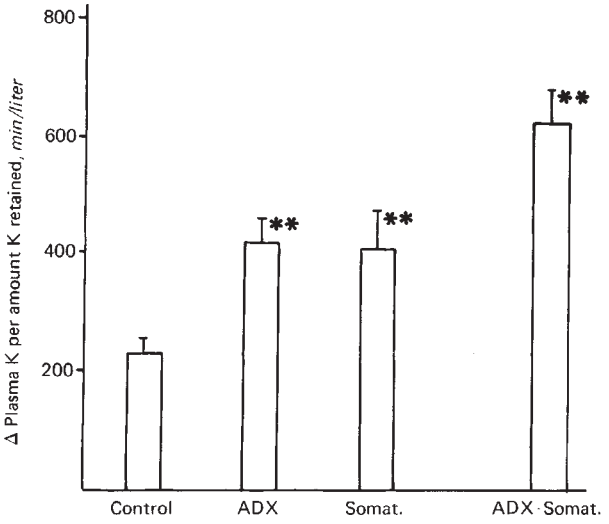

Fig. 3. *The rise in plasma potassium concentration per amount of potassium retained in control animals, adrenalectomized rats (ADX), insulinopenic rats (Somat), and rats with combined insulinopenia and adrenalectomy (ADX-Somat).* All values represent the mean ± SEM. Two asterisks (**) indicate $P < 0.005$ compared with the value in control rats.

tassium chloride administration. Despite the excretion of an identical percentage (47%) of the administered potassium load in both control and adrenalectomized rats, the increment in plasma potassium concentration was significantly greater in adrenalectomized rats. Thus, the decreased potassium tolerance in adrenalectomized rats must be attributed to impaired tissue uptake of potassium. Whether the defect is the result of aldosterone deficiency or is due to a deficiency of some other adrenal hormone is not answered by the present study. It is known that adrenalectomy in rats reduces the amount of circulating epinephrine to very low levels [26], whereas norepinephrine levels remain relatively normal. It is also known that beta agonists can enhance cellular uptake of potassium [27, 28] by liver and skeletal muscle [28]. More recently, Lum and Lockwood [29, 30] have shown that epinephrine and other beta agonists (but not alpha agonists) exert a protective effect against hyperkalemia in cats infused simultaneously with potassium chloride. The protective effect of epinephrine was not altered by prior nephrectomy or pancreatectomy, indicating that this effect was not dependent on renal potassium excretion or the presence of insulin. Thus, the current findings could also be explained by a deficiency of epinephrine. Because all animals received physiologic replacement doses of dexamethasone, it is unlikely that insufficient glucocorticoid replacement can explain the persistent defect in potassium metabolism. In addition, the impairment in cellular uptake of potassium could not be attributed to acidosis in adrenalectomized animals, because blood pH was similar to controls and did not change during the study. Last, although considerable controversy exists concerning the actual intracellular potassium content of adrenalectomized animals [17, 31], it is conceivable that the extrarenal defect was caused, in part, by an elevation in tissue potassium content in the adrenalectomized rats.

Although the inability to dispose of an acute potassium load in adrenalectomized rats appears to be due mainly to an extrarenal defect, the data also suggest that adrenalectomized rats may have a subtle impairment in renal potassium excretion. Thus, although the adrenalectomized rats were in potassium balance prior to the clearance study (24-hour urinary potassium excretion = dietary intake) and displayed baseline potassium excretion rates that were similar to those of control animals, this level of potassium excretion was achieved at the expense of a slightly, but significantly elevated baseline plasma potassium concentration. This observation is consistent with a mild defect in chronic renal potassium homeostasis in the adrenalectomized rats. Previous studies have shown that urinary potassium excretion varies directly with the plasma potassium concentration during potassium loading [32]. The present study demonstrates that this direct relationship is present even in adrenalectomized rats that have been totally depleted of mineralocorticoid activity. The slope of the line relating urinary potassium excretion to plasma potassium concentration in adrenalectomized rats tended to be less, however, than it was in controls (group 5), which had a similar rate of sodium excretion. These data are compatible with but do not conclusively document a defect in renal potassium excretion following acute potassium loading in adrenalectomized rats. It is unlikely that this apparent defect in renal potassium excretion, present in adrenalectomized rats, can be explained by a fall in GFR during the study, because GFR was reduced to a similar extent (14 to 21%) in all groups. Furthermore, it is well known that urinary potassium excretion is relatively independent of GFR [33].

Results from previous studies clearly demonstrate an impairment in potassium homeostasis following adrenalectomy in all species examined [7, 8, 20, 36, 37]. The site of the defect (renal vs. extrarenal), however, has not been clearly delineated. In studies where decreased renal potassium excretion has been demonstrated in adrenalectomized ani-

mals [8, 20], the animals were frequently not replaced with volume or glucocorticoids and the blood pH was not monitored. It is possible that changes in systemic and/or renal hemodynamics secondary to volume contraction could have contributed to the defect in potassium excretion. In contrast, the current findings indicate that, in glucocorticoid and volume-replaced adrenalectomized rats, the inability to dispose of an acute potassium load is primarily due to an extrarenal defect resulting from an absence of aldosterone or some other adrenal hormone.

Following somatostatin-induced insulinopenia, a significant decline in acute potassium tolerance was also observed, despite the renal potassium excretion that was similar to control rats. These findings suggest that somatostatin administration, like adrenalectomy, is associated principally with an impairment in the extrarenal mechanisms of cellular potassium uptake. Previous results from our laboratory have demonstrated that somatostatin induces a similar impairment in acute potassium tolerance in dogs [5] and that this can be corrected by replacement of basal insulin levels alone. Thus, the defect in potassium tolerance following somatostatin has been shown to be secondary to the resultant insulinopenia. No significant defect in renal potassium excretion was observed in insulinopenic rats. When the increase in urinary potassium excretion was related to the increase in plasma potassium concentration, the slope of the line in somatostatin-infused animals (1.55 ± 0.34) was similar to controls (1.64 ± 0.33). These results suggest that insulin has no direct effect on renal tubular potassium secretion and that the changes in urinary potassium excretion following somatostatin-induced insulinopenia and exogenous insulin administration [16] are the consequence of changes in plasma potassium concentration brought about by insulin's action on extrarenal tissues.

When somatostatin was infused into adrenalectomized rats to bring about combined insulin and adrenal hormonal deficiency, the defect in potassium tolerance was greater than it was with either somatostatin or adrenalectomy alone (Fig. 2). The rise in plasma potassium occurred earlier and remained elevated for a more prolonged period of time, resulting in an integrated rise in plasma potassium concentration above basal that was significantly higher in these animals with combined deficiency compared to those with either insulin or adrenal insufficiency alone. Renal potassium excretion in this group (group 4), as well as the percent of the administered potassium excreted within 2 hours, was similar to control rats.

Statistical differences in potassium tolerance between animals with adrenal or insulin insufficiency alone compared with those with combined deficiency were also demonstrated when the incremental rise in plasma potassium concentration above baseline was factored by the amount of potassium retained. This expression yields a more specific index of extrarenal potassium tolerance. As can be seen in Fig. 3, the defect in extrarenal potassium tolerance was similar in adrenalectomized and insulinopenic rats, both groups exhibiting a significantly greater rise ($P < 0.005$) in plasma potassium per amount of potassium retained compared to control rats. The greatest rise in plasma potassium concentration per amount of potassium retained occurred in animals with combined adrenal and insulin insufficiency where the rise was significantly greater than that occurring in animals with either adrenalectomy alone or insulinopenia alone. Thus, the combined effects of adrenal and insulin deficiency produce a degree of extrarenal potassium intolerance that is greater than that occurring with either adrenal or insulin deficiency alone.

The combined effects of insulinopenia and adrenal hormone deficiency in producing impaired cellular potassium uptake may have particular clinical relevance because hypoaldosteronism is known to occur with increased frequency in diabetic subjects [1, 2] and the combination may lead to potentially fatal hyperkalemia [34]. Only one previous study has examined the ability of diabetic subjects with hypoaldosteronism to dispose of an acute potassium load [35]. Although these diabetics demonstrated a slight decrease in renal potassium excretion compared with controls, the difference was not statistically significant and the rise in plasma potassium concentration following acute potassium loading could not be explained by the marginal renal defect. These results are consistent with the present findings and suggest that a large part of the hyperkalemia in diabetics with hypoaldosteronism is due to a defect in extrarenal potassium homeostasis.

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